

Historical and contemporary views on cholera transmission: are we repeating past discussions? Can lessons learned from cholera be applied to COVID-19?

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Cholera, a devastating diarrheal disease that caused several global pandemics in the last centuries, may share some similarities with the new COVID-19. Cholera has affected many populations in history and still remains a significant burden in developing countries. The main transmission route was thought to be predominantly through contaminated drinking water. However, revisiting the historical data collected during the Copenhagen 1853 cholera outbreak allowed us to re-evaluate the role of drinking-water transmission in a city-wide outbreak and reconsider some critical transmission routes, which have been neglected since the time of John Snow. Recent empirical and cohort data from Bangladesh also strengthened the dynamic potentiality of other transmission routes (food, fomite, fish, flies) for transmitting cholera. Analyzing this particular nature of the cholera disease transmission, this paper will describe how the pattern of transmission routes are similar to COVID-19 and how the method of revisiting old data can be used for further exploration of new and known diseases.

Key words: Cholera transmission; Bangladesh; COVID-19; pandemic; drinking water; F-diagram; Fecal–oral transmission.

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Cholera, a diarrheal disease caused by bacteria, has shaped human history for centuries, while COVID-19 is a newly emergent respiratory disease caused by the SARS-CoV-2 virus. Despite their apparent differences, there are some surprising similarities between the two diseases. For example, both appear to spread most easily under crowded conditions where close, prolonged, personal contact is frequent and social distancing is not possible or followed. Due to the recent emergence of SARS-CoV-2, researchers often find themselves lacking critical data about the disease, and it falls upon the research community to explore how and where historical data can be used to fill these research gaps. To this end,

cholera has taught us the value of looking backwards to guide the path forward, and historical data have allowed contemporary researchers to address long-simmering uncertainties regarding cholera transmission. Therefore, this paper will try to provide insight into some possibly overlooked routes that may influence primary cholera transmission by using both historical and new data, and to further examine the similarities of these findings to developing COVID-19 transmission knowledge.

FROM THE SEVEN PANDEMICS TO TODAY

The fear of cholera has, for several centuries, been one of the drivers behind modern city planning, the

demand for adequate living spaces, and better hygiene, clean drinking water, and sanitation. Currently, an estimated 1.3 billion people are at risk of cholera globally, with 1.3 to 4 million cholera cases occurring annually, which result in approximately 21 000–143 000 fatalities per year (1). Exact figures are difficult to estimate as many cases go unreported due to political and/or economic reasons (such as fear of repercussions on trade and tourism) or simply to the lack of diagnostic capacity in remote and less economically fortunate areas (2).

Cholera is a severe diarrheal disease caused by the O1 and O139 strains of the bacterium *Vibrio cholerae* and is endemic to the brackish waters in the estuaries of the Ganga and Brahmaputra rivers in the Bay of Bengal (3–5). While the first written records of the disease in South Asia date back to the Hindi Vedas from 500 BC, the history of cholera suggests the rest of the world did not know it before 1817. However, 1817 is the year where the first of at least seven different O1 pandemics spread from the Bay of Bengal (6). The current seventh, and still ongoing, pandemic started in 1961, although not in the Bay of Bengal, but in Sulawesi, Indonesia. In 1992, a new strain, O139, emerged in India. After it caused a significant epidemic in a population that was mostly immune to the O1 – but not the O139 – serotype, it now resides in Asia and, for unknown reasons, has not spread to the rest of the world (7).

Despite its legacy as a lethal disease, with a 25–50% mortality rate in untreated cases, cholera is not always a catastrophic public health threat where it is endemic (8), as proper medical attention can lower the mortality rate to < 1%. The primary and non-costly treatment of cholera consists of replacing lost fluids using oral and intravenous-administered fluid containing electrolytes (up to 1 liter per hour). The rice-water stools excreted by symptomatic individuals are highly contagious, and a person can excrete as many as 2×10^{12} *V. cholerae* bacteria in a day (9). Volunteer trials have shown that the infectious dose for severe diarrhea is 10^8 – 10^{11} bacteria in healthy persons. The infectious dose drops to 10^4 – 10^8 when a bicarbonate buffer is used to neutralize the stomach acid shortly before inoculation, and foods such as rice, fish, custard, and skimmed milk may act as an acid buffer (10). However, as many as 50% of people infected with *V. cholerae* will never experience severe diarrhea and (depending on immunity, inoculum dose, etc.) will only have mild symptoms or be asymptomatic, although they will still be able to carry and excrete the bacteria in smaller concentrations (10). As a consequence of the high bacterial load and volume of rice-water stool excreted, cholera

disproportionately affects people of low socioeconomic status who live in overcrowded, unhygienic conditions with insufficient water and sanitation facilities (8). For this reason, the disease is considered an indicator of economic inequity and a lack of social development.

THE IMPACT OF JOHN SNOW

One name that is closely tied to our understanding of cholera transmission is Dr. John Snow who, in 1854, during the third cholera pandemic in London, removed the handle of the Broad Street water pump and thus stopped the outbreak, although the outbreak had peaked and was already receding when the handle was removed. In a separate study, Dr. Snow further showed mortality differences in households from the same street, but connected to different waterworks. The two waterworks in operation were both receiving water from the Thames river, but had different qualities. The Lambeth water company inlet was upstream of London's sewage outlet, and their customers had a mortality rate of 37/10 000, while the Southwark and Vauxhall Company harvested the polluted water downstream with a mortality rate of 315/10 000 (11). These findings linked water quality to mortality and, essentially, ended the contemporary arguments regarding whether contagions or miasmas were the causes of disease (12). The legend of the pump handle has had an effect on how Dr. Snow's findings are remembered, with the linkage between cholera and contaminated drinking water carved in stone ever since. His other findings concerning cholera being linked through person-to-person and food transmissions appear to have receded into the background. Even today, short-cycle transmission (through personal household contact and hygiene) is under-researched in comparison with long-cycle transmission (e.g., drinking water) (13).

Cholera can be grouped into two general and interconnected transmission routes: the aquatic reservoir to host route (*V. cholerae* that has survived and replicated itself outside of a human host in the aquatic environment and subsequently transmitted to a human host – often referred to as primary transmission), and the fecal–oral route (transmission from one human host to another – often referred to as secondary transmission) (14). Cholera outbreaks in non-endemic areas such as in London and Copenhagen in the 1850s are considered to involve only secondary transmission (with the potential exclusion of the index case), whereas cholera outbreaks in endemic areas such as in Bangladesh involve both primary and secondary

transmission (8). Despite being researched for decades, the importance of the main drivers behind *V. cholerae* primary transmission in Bangladesh remains disputed, and if potential transmission routes are not fully explored and understood, the control of the disease can never be achieved.

NEW HISTORICAL INSIGHT INTO TRANSMISSION AND THEIR POSSIBLE IMPLICATIONS

The notion that cholera is closely linked to drinking water might have been different if John Snow had lived in Copenhagen in the summer of 1853, where an outbreak killed more than 4663 people (3.4% of the city's population) (15). While no study has specifically investigated its transmission, most historians have assumed the outbreak to be drinking water-driven based on Snow's Broad Street pump findings. The Copenhagen outbreak was unique in an epidemiological sense as the city's population had never previously been exposed to *V. cholerae*. In the middle of the nineteenth century, Denmark still had quarantine legislation that had been developed during the time of the plague. It specified rules for the quarantine of ships arriving from ports infected by certain epidemic diseases, cholera among them. However, in 1852 the quarantine rules for cholera were lifted due to a change in medical thought, whereby most authorities decided the disease was miasmatic and, as such, the quarantine rules no longer made sense (16).

At the time of the outbreak, Copenhagen had a population of approximately 130,000 people and a considerable number of cows, pigs, horses, and other livestock confined to small, filthy spaces behind the city's ramparts. It was not uncommon to see cows permanently living on the first floors of city houses, as they were kept to eat the waste products from beer production. There was no sewage system, and all solid and liquid wastes were temporarily stored in cellars or went directly to the open gutters flowing through the city and emptying in the harbor, part of it into the canal in front of the castle and fish market (16).

Copenhagen had several independent water supplies, all constructed from hollow oak tree pipes connected by lead joints. In these, the water was neither treated nor filtered and was free-flowing (by gravity in non-pressurized systems) from the surrounding lakes to the city. However, one water supply harvested water from a lake 7 km away from a height of 30 meters above sea level, which fed the only water fountain in Copenhagen with pressurized water (17). Leaky lead joints connecting the

pipes allowed wastewater from the gutters in the streets above to enter the pipes and, hence, the drinking water. This was revealed in the newspapers where people complained about the water quality as being filthy, with eels, fish, and other creatures found in it (18).

In 2018, a project at the University of Copenhagen modeled the cholera outbreak and paired it with a GIS overlay of the different water-distribution companies (see Fig. 1) (19). If the pipes were the conveyor of the disease, cholera would be expected to have moved with the water flow. The lack of this suggests a short-cycle transmission within the secondary transmission route in Copenhagen. While the drivers of this transmission remain unknown, congested housing, lack of hygiene, and possible food contamination are qualified guesses. Unfortunately, after 167 years, it is not possible to investigate the importance of the different transmission routes further. However, in Bangladesh, the physical environment, in terms of crowding and low hygiene housing, is similar to what could be found in 1853 Copenhagen and London in 1854.

INVESTIGATING TRANSMISSION ROUTES IN BANGLADESH USING HISTORICAL OUTBREAKS

The conditions (water temperature, pH, salinity, and plankton blooms) within the estuaries and in the Bay of Bengal favor *V. cholerae* survival and growth at or around the same periods as seasonal peaks are observed in the annual 100 000 cholera cases in parts of Bangladesh (3, 21–23). Therefore, researchers have investigated whether the contamination of drinking water from an aquatic reservoir was the main route of cholera transmission in Bangladesh (3, 22, 24), either by drinking water drawn directly from the rivers during the dry season, or by drawing from water wells that were flooded in the monsoon season. Conversely, King et al. (25) used mathematical modeling to argue that free-living *V. cholerae* in the aquatic reservoir was responsible for relatively few numbers of cholera cases. Their study suggested that previously underestimated numbers of mild or asymptomatic cases hold the key to interpreting the patterns of disease in Bangladesh.

FROM AQUATIC RESERVOIR TO HOST IN BANGLADESH (PRIMARY TRANSMISSION)

Aquatic reservoir

In Bangladesh, *V. cholerae* can be extracted from aquatic reservoirs through water and fish (3, 26). In

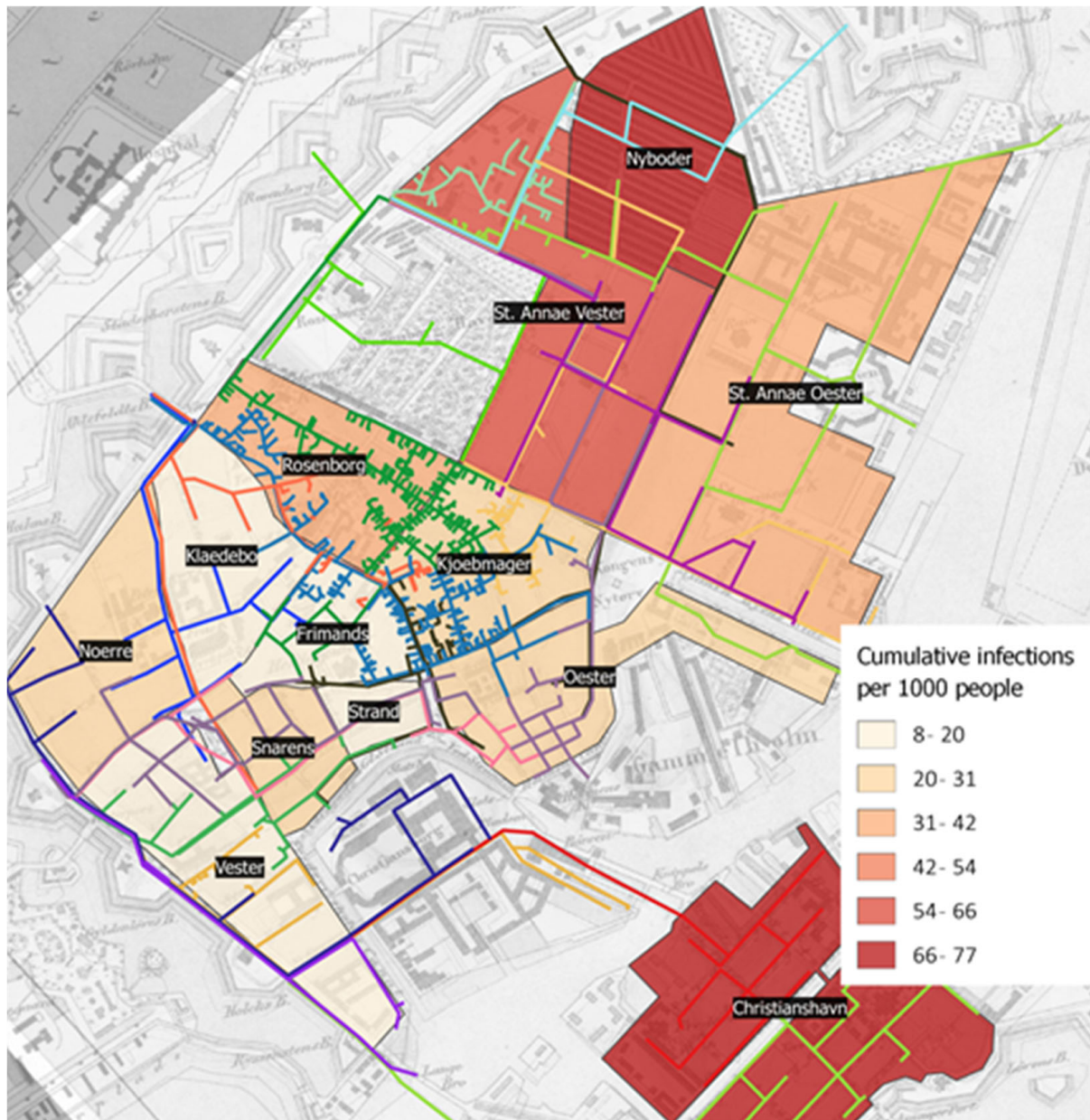


Fig. 1. The different water companies pipes (different colored) followed the gradient (not shown) of the landscape and flowed from the lakes towards the harbor and the castle (from upper left corner diagonally to the lower right), while cholera crossed the pipe networks and moved horizontally (upper right to lower left) in the city (20).

other countries, water plants and water birds have also been suggested as potential extraction points (8, 24, 27).

To become infected with cholera from an aquatic reservoir, a host needs to ingest *V. cholerae* via water (such as through consuming contaminated drinking water, or bathing/swimming in a contaminated river and ingesting some of the

water), food, contact with fomites (such as kitchen utensils) or direct oral contact with his/her hands (e.g., a person may eat with contaminated hands). Thus, we can ask, what is the link between the points where *V. cholerae* can be extracted from an aquatic reservoir and the points where it can be ingested by the host? (Fig. 2).

Water extracted from the aquatic reservoir for drinking water

Given the distinct seasonal patterns of cholera cases in Bangladesh, researchers have investigated whether there are seasonal introductions of *V. cholerae* into the drinking water directly from the aquatic reservoir (3, 21, 22, 29, 30). Every year, low river flow during the dry season leads to an intrusion of saline water from the Bay of Bengal into the coastal regions, creating river environments conducive to *V. cholerae* survival and growth. Some studies have suggested these conditions spark the coastal dry season outbreaks once people ingest contaminated water originating from the aquatic reservoirs (3, 21). As the dry season progresses, saline water intrudes further inland and, with the aid of copepods, *V. cholerae* migrates to the inland areas. During the monsoon season, floodwaters carry *V. cholerae* from the rivers to the inundated inland regions where it then proliferates in water-logged areas. Research has suggested that the flood waters contaminate water sources, including ponds and wells used for drinking water, thereby driving the post-monsoon outbreak in the inland areas (3).

The rivers could be a direct transmission route from the aquatic reservoir to the host, but only if high salinity water was found to be consumed by the local population (8). Unsurprisingly, however, Bangladeshis tend to choose drinking water that has an authentically pleasing taste (23). Therefore, would people in Bangladesh drink water directly

from a high salinity aquatic reservoir? To answer this question, Grant et al. (31) conducted a simple taste experiment investigating whether a local population from the coastal region of Bangladesh had the tolerance to drink water with a salinity similar to that which is found in the rivers during the low flow season. It was further investigated whether they would continue to drink from a water source after it had been flooded and contaminated with brackish river water during the monsoon season. The results for both scenarios were negative, indicating that there might be other, or parallel, routes of transmission.

Cholera transmission via the consumption of fish

Studies outside Bangladesh have found associations between cholera and the consumption of under-cooked shellfish (8, 24, 32). However, in Bangladesh, most shellfish are exported, expensive for poor households, and harvested during periods that do not coincide with the cholera seasons (33). Therefore, while it is plausible that some cases could occur through this route, it is unlikely to be the driving force behind the large seasonal outbreaks observed in the Bangladeshi context.

To investigate the possible transmission via fish, a study in 2018 found a high prevalence of *V. cholerae* in the gills, rectum, intestines, and scales of the Hilsa fish – a commonly caught and consumed fish in Bangladesh that lives in both freshwater and

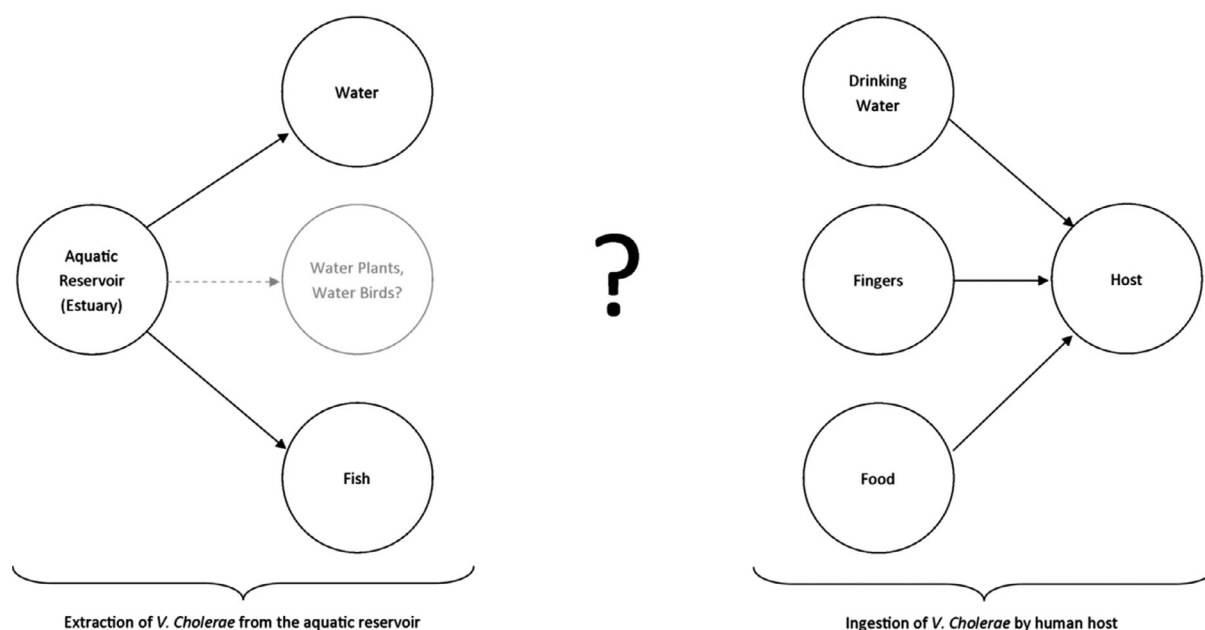


Fig. 2. Cholera's possible primary transmission routes in Bangladesh, from the aquatic reservoir to the host (28).

seawater (26). In 1951, Pandit and Hora had mentioned Hilsa fish as a possible link, but their results were not investigated further (34). Hilsa fish migrate up the rivers from the Bay of Bengal twice a year, from July to October and January to March, which corresponds to the two seasonal peaks in cholera cases (29). This suggests that Hilsa fish may potentially serve as a vehicle of transmission for *V. cholerae* (26). Furthermore, during these periods, the availability of Hilsa fish in the local markets increases, resulting in lower prices. In contrast, during other times of the year, the prices are generally too high for poor households (26). Fish in Bangladesh is cooked or fried before eating and, therefore, cannot serve as a direct transmission route. However, they could represent a possible missing transmission link: unhygienic conditions within the kitchen environment and consequent kitchen transmission.

Unhygienic conditions within the kitchen environment as a potentially overlooked transmission link

In Bangladesh, studies have shown that the kitchen environment could be contaminated through the cleaning and gutting of contaminated fish (26), or through the use of contaminated river or canal water for domestic purposes (34). Likewise, using domestic water contaminated with *V. cholerae* on prepared food and vegetables that are eaten uncooked has also been linked to cholera transmission (35).

In Bangladesh, fish is generally purchased whole in the local markets and then taken home to be cleaned and gutted. This is often done on the floor of kitchen areas. Utensils, including a large stationary cutting knife (called 'boti'), are typically used for cutting uncooked fish and other food in the kitchen (26). In a hygiene study by Hussain et al. (36), a considerable amount of *E. coli* contamination was found on botis and washed food plates. Other studies have suggested that the unhygienic handling of fish may be another factor leading to *V. cholerae* transmission (8, 24). Scheelbeek et al. (37) suggested that in conditions where kitchen hygiene is limited, there is a higher risk of cholera transmission from cleaning fish than from consuming them.

Once *V. cholerae* is present in the kitchen environment, unhygienic conditions may allow for the cross-contamination/recontamination of food and water through multiple routes. For example, one study found that *V. cholerae* survived on fomites typically used in kitchen environments for 1–4 h in a culturable state and up to 7 days in a viable but non-culturable state (i.e., still infectious but unable

to reproduce) (38). A limited amount of available water in the kitchen environment may restrict people's ability to engage in safe hygiene practices such as hand washing or thoroughly cleaning kitchen tools/utensils (39), thereby increasing the risk for cross-contamination of *V. cholerae* from fomites to food and/or water and, ultimately, transmission to a new host.

THE FECAL–ORAL ROUTE (SECONDARY TRANSMISSION)

To further understand fecal–oral transmission, in 1958 Wagner and Lanoix (40) developed the F-diagram, illustrating how a pathogen may be transmitted from feces to a new host through fingers, flies, fields, fluids, and food. Within the F-diagram, each element represents the transmission route of the pathogen. In the finger route, pathogens are transmitted from the original host's feces to food or directly to a new host via hand contact. Systematic reviews have supported these results by finding that hand washing with soap has a protective effect against diarrhea diseases (41). However, studies in Bangladesh have shown that, among cholera patients, there is a low frequency of hand washing with soap (7%) after toilet visits (42). Flies can also act as vectors that carry bacteria by first landing on feces and then on food. A study conducted in a slum area of Dhaka confirmed the transmission of *V. cholerae* by flies in a real kitchen environment and quantified *Escherichia coli* transmission during food preparation, which showed a magnitude of 600 *E. coli* deposited in 50% of the landings (43, 44). In the field route, the transmission of pathogens may occur when untreated feces are used as fertilizer or wastewater is used for crop irrigation (45). The fluid route can be divided into drinking and domestic water such as water used for cooking, personal hygiene, and household cleaning. The drinking-water route is relatively straightforward, and occurs when a drinking-water source is contaminated by feces containing *V. cholerae* and is then consumed by a new host. However, one limitation of the F-diagram is that it does not account for possible recontamination (contamination occurring within the household) of drinking water that has been previously treated or collected from a 'clean and safe' source when it is drunk from a dirty glass or stored under unhygienic conditions (46, 36).

Evidence has also been found that *V. cholerae* can survive for long periods, and even replicate, on food under the right conditions (7). In Bangladesh, cholera transmission has been associated with

uncooked vegetables as well as prepared foods such as cooked rice and chicken, when these food items have come into contact with contaminated fingers, flies, or fluids (47).

The Copenhagen transmission was secondary, while the outbreaks in Bangladesh have a primary source. However, we can use the analysis of historical, secondary transmission in the analysis of primary transmission, especially when we understand that other, non-drinking, water-borne transmissions might be important. This idea leads us to Fig. 3, which illustrates where primary and secondary transmission can be interrupted.

Fighting cholera is about disrupting *V. Cholerae* transmission routes, and Fig. 3 provides an overview of where and by what means such transmission routes can be broken. As illustrated, a successful intervention likely involves different approaches, but first, the routes need to be qualified in terms of their relative importance in bacterial transmission to evaluate the possible effect of the intervention. While these lines of disruption are specific to Bangladesh in terms of water use and habits, they are based on a historical approach using the data from Copenhagen in 1853. To definitively distinguish and quantify the specific transmission route in which a host has become infected with *V. cholerae*, a thorough investigation using microbiological testing and contact tracing is required. However, in lower-income settings such as Bangladesh, this is rarely possible.

John Snow showed that water quality is important. However, by looking at infectious doses, it is also clear that only heavily contaminated water is able to make healthy people ill. In contrast, only 0.1% of the *V. cholerae* infectious dose in drinking water is needed if it is ingested via food. Therefore, it is essential to revisit the original ideas of John

Snow, and not simply focus on water quality. This means enlarging the focus to include the house, and especially kitchen hygiene, even though improvements in housing standards and kitchen upgrades are more expensive than simply chlorinating the water supply.

HISTORICAL SIMILARITIES TO COVID-19

Despite the dissimilarities in the causes of COVID-19 (a zoonotic virus) and cholera (bacteria), there are several similarities that can be observed. First, both are seen as society-disrupting, Asian-origin diseases spreading out to the rest of the world. Second, neither disease is entirely new in the sense that human coronaviruses, and the original O1 cholera type, are known diseases with considerable immunity among previously exposed populations. However, after their initial appearances, the continuous evolution of the SARS coronavirus and *V. cholerae* created new outbreaks, and both SARS-CoV-2 and O-139 have quickly become new threats to public health. Moreover, numerous asymptomatic carriers make the fight against both diseases more challenging.

Is COVID-19 is a poverty-driven disease? Cholera is known to be a disease of poverty, and current data have indicated that COVID-19, despite being able to cause worldwide infections across socioeconomic boundaries, tends to have a higher mortality rate in lower-income populations (48, 49). As these population groups have a tendency to live in overcrowded conditions where social distancing and high hygiene levels are impossible to maintain (50). Therefore, compliance with typical public health advice on how to reduce the spread of the virus is likely to be low among these

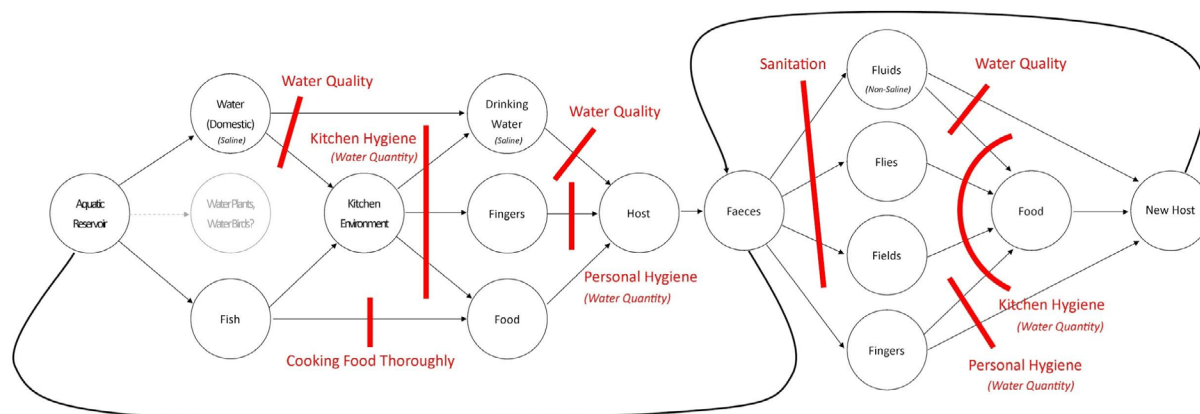


Fig. 3. Cholera's primary (reservoir to host) and secondary (feces to new host) transmission routes in Bangladesh, with redlines as indicators for possible interventions (28).

populations. However, infrastructural risk factors, that is, hygiene and housing, are not the only risks. Access to health care and the presence of under-treated, non-communicable diseases such as diabetes, which has a higher prevalence among lower socioeconomic groups (51), are other factors to be taken into consideration. Both COVID-19 and cholera have had and will have the potential to change future living conditions, the way we interact, and especially how we plan and build future standards for living/work space and hygiene.

As to the possible fecal–oral transmission of SARS-CoV-2, it remains unclear. While live virus has been detected in many infected patients' stool samples (52, 53), it is uncertain if it remains infectious. Present knowledge regarding the spread of COVID-19 via fields and fluids is also limited, and the contribution of fomites and flies is currently being investigated (54–58). The presence of SARS-CoV-2 in wastewater has also been widely discussed (59). However, no infectious virus has been detected in either untreated or treated sewage, or in drinking-water supplies.

The importance of airborne transmission of SARS-CoV-2 and, specifically, the importance of transmission via droplets vs. aerosols (60) illustrate a key challenge for both diseases. That is, although we can recognize contamination routes, we are not fully aware of their relative importance, that is, which routes are the most potent in terms of the flow of pathogens and the actual infective dose, and which ones exist but are insignificant from a broader public health perspective (61). Perhaps the clue to answer most of our current questions regarding cholera and COVID-19 does not lie entirely within new investigations, but in looking back and re-analyzing the vast amount of data that has been collected in the past.

Hopefully, this paper will inspire researchers to revisit the old epidemics and learn from them, as now, when time is of the essence, is the moment to stand on the shoulders of our forebearers and look not only at their discoveries, but also at their compiled work, because 'people will not look forward to posterity who never look backward to their ancestors'. – *Edmund Burke*.

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